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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,560	06/23/2003	James W. Darrow	CGI-0004	1258

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EXAMINER	
TUCKER, ZACHARY C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,560	DARROW ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,9,10 and 14-32* is/are pending in the application.

4a) Of the above claim(s) *5,9,10,14,16-20,24-26 and 28-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,15 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *27Jan05,8Dec03,11Aug03*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

As requested in the correspondence from applicants filed 27 January 2005, which is in reply to the Requirement for Restriction mailed 27 December 2004, claims 5, 7, 9, 10, 14-16, 18 and 20 have been amended, new claims 21-32 added, and claims 1-4, 6, 8, 11-13 cancelled.

Election/Restrictions

The Requirement for Restriction mailed 27 December 2004 set forth two groups, one Group drawn to chemical compounds and a pharmaceutical composition comprising the compounds, and the other Group drawn to processes of using the compounds, as in methods of treating diseases, and a method for identifying a kinase.

Applicants' amendment necessitates that the Groups be set forth again for the sake of clarity:

Group I, drawn to chemical compounds and a pharmaceutical composition comprising said compounds, claims 5, 7, 9, 10, 14, 15, 21-27.

Group II, drawn to methods of treating various diseases and a method of identifying a kinase, claims 16-20 and 28-32.

Applicant's election with traverse of Group I in the reply filed on 27 January 2005 is acknowledged. The traversal is on the ground that the Requirement is improper due to the methods not being practicable with any other agents besides the exact agents claimed, and furthermore that no serious burden on the examiner is posed by searching

all of the claimed subject matter. By this reasoning, no restriction between a product and a process of using that product could ever be proper.

This is not found persuasive because the method of use claims are drawn to methods of treating, for example cancer. This method is accomplished by the step of administering a compound according to the invention. Therefore, the object of the method is the treatment of cancer. This object is achievable by administering therapeutic agents materially different from those claimed.

Also, condition "(B)" of the two rationales for a showing of distinctness between a product and a process of using that product is met by virtue of the showings herein that products claimed in the application have other materially different uses, such as intermediates for the synthesis of UV-absorbing compounds (Cavalier et al). This was not known until a prior art search was commenced.

Insofar as search burden is concerned, a showing of separate classification is a showing of search burden. Applicants argue that no serious search burden exists. According to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has made no rebuttal of the examiner's showing of separate classification and separate status in the art. Thus, a serious burden has been established.

It must be noted that medical methods of treatment require a considerable amount of searching in order to ascertain the level of ordinary skill in the art with respect to the first paragraph of 35 U.S.C. 112. This additional search is not required in a survey of the chemical literature for simple disclosures of compounds. The search required for determination of patentability of the methods of treatment in the instant application is of a different scope than the search required only for determination of the patentability of the compounds claimed.

In any case, applicants are reminded that when the compounds according to the elected Group are deemed allowable, the methods in Group II will be rejoined and examined.

There is also a requirement for an election of species for examination operative in the instant case, and applicants have elected the compound N3-(2-methoxybenzyl)-5-(4-phenoxyphenyl)-pyrazine-2,3-diamine for a starting point for the prior art search of the compounds. This compound is designated "(5)" and appears at page 25 of the instant specification.

A genus based on this compound was searched, and no art anticipating or rendering obvious the same was found, after which art was found in applicants' submission of the Information Disclosure Statements filed 27 January 2005, 8 December 2003 and 11 August 2003. Allowable subject matter is indicated *infra* in the section headed "Allowable Subject Matter."

Claims 16-20 and 28-32 are withdrawn as being drawn to nonelected inventions.

Claims 5, 9, 10, 14, 24, 25, 26 and 27 are further withdrawn as not readable on the elected species.

The examiner has noted that applicants' counsel indicated claims 14 and 16, which specify the IC_{50} of a compound according to the instant claim, in some unspecified protocol of *in vitro* kinase modulation as being less than or equal to 25uM, assay do not read on the elected species.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 and 15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21, the independent claim, recites "crystal forms" of a chemical entity of formula (1).

Absent some identifying information, particularly x-ray powder diffraction spectrum data, or at least a single crystal x-ray diffraction spectrum, the recitation of "crystal forms" is redundant. Crystal forms of chemical entities of formula (1) are within the scope of the claim as drafted, without the recitation of "crystal forms."

No definition of this term appears in the specification.

If the recitation of "crystal forms" is intended to embrace certain special or unusual crystal forms, more information describing that special crystal form is needed.

Interpreted this way, the claim is indefinite. That is, by reciting "crystal forms" in the claim, applicants are implying that some multiple special crystal polymorphs are being claimed, while no information necessary to describe those polymorphs is being supplied. Thus, the claim is indefinite.

If no special crystalline polymorph is claimed, then the phrase "crystalline forms" is superfluous and should be removed, because it is understood that a crystalline solid form of the chemical entity of formula (1) is in fact covered by the claim.

Claim 21 has been examined on the merits as though "crystal forms" were not recited therein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of chemical entities having the formula (1) or pharmaceutically acceptable salts, hydrates and diastereomers thereof, does not reasonably provide enablement for the full scope of all prodrugs of a chemical entity having the formula (1), and therefore does not provide enablement for a pharmaceutical composition comprising the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the full scope of the invention specified in instant claims 21-23 and 15.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claim 21, from which claims 22, 23 and 15 depend, is limited to chemical entities of formula (1) having the structure depicted, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of chemical entities having the formula (1) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only acylated derivatives, which are commonly cited as examples, and suggested as the preferred type of prodrug on page 15 of the instant specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily depend on the identity of the pharmacologically active agent formed from the prodrug

for patentability. A prodrug is not necessarily even structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a chemical entity having the formula (1) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound

will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically derived when the compound in question is an allegedly novel compound, as are chemical entities of formula (1).

(F) The following passage is the direction provided for the synthesis of prodrugs of chemical entities of formula (1). –

> [0041] The present invention also encompasses the prodrugs of the compounds of Formula I, for example acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable acylated and other prodrugs of the compounds encompassed by Formula I.

No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than acylated derivatives.

(G) No working examples, out of the seven preparative examples, of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of chemical entities having the formula (1), a complete structure activity analysis of all of the entities falling within formula (1) would have to be completed. This

analysis would involve thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active chemical entities of formula (1) *in vivo* identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the chemical entities having the formula (1), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the chemical entities having formula (1) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making

prodrugs of chemical entities having the formula (1), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

Claims 21-23 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling chemical entities of formula (1), pharmaceutically acceptable salts, hydrates and diastereomers thereof, does not reasonably provide enablement for solvates of those compounds, and therefore, compositions comprising said solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making the determination of whether certain embodiments of a claimed invention are enabled by the disclosure, the Office relies on the following factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Insofar as the solvate embodiment of claims 21-23 and 15 is concerned, those claims read on solvates of chemical entities according to formula (1) and a pharmaceutical composition (claim 15) comprising solvates of chemical entities according to formula (1). The scope of the solvates recited in the claims includes solvates of a chemical entity according to formula (1), with *any* solvent. The definition of

a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug."

(B) The nature of the invention is that of a solvate with any solvent of a chemical compound and a pharmaceutical composition comprising that solvate.

(C), (D), (E) Solvates, at the time the invention was made, were known, but not to such an extent that the directed preparation thereof was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of

the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formula (I) is even possible (see Gavezzotti, page 309, point #1).

(F) There does not appear to be any mention of solvates in the specification, so no guidance for the preparation of a solvate is in the disclosure.

(G) No working examples of the preparation of any solvate is in the disclosure.

(H) Each chemical entity of formula (1), of which there are thousands, as a solvate with every solvent within the scope of "solvate" generally, of which there are also thousands, represents the efforts of many over a period of years. Those efforts are potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. Applicants' right to exclude others from making solvates of compounds according to formula (1) is unwarranted in light of the complete lack of any direction as to how one of ordinary skill would do so.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

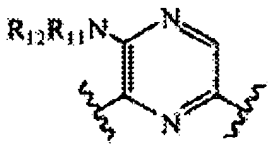
A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Cavalier et al, "Catechol Derivatives of Aminopyrazine and Cell Protection Against UVB-Induced Mortality" Bioorganic and Medicinal Chemistry, vol. 9, pages 1037-1044 (April 2001).

At page 1039, in Scheme 4, Cavalier et al discloses compounds 6e and 6g, which are starting materials for synthesis of UVB absorbing compounds. These two compounds anticipate claims 21-23 where:

Both m=0; Z_1 and Z_2 are both –NH-; R_1 is phenyl, substituted with one or two hydroxyls; R_2 is phenyl, substituted with one hydroxyl; M is:



, where R_{12} and R_{11} are both hydrogen.

The proviso at the end of the definition of R_1 and R_2 in instant claim 21 does not exclude Cavalier et al's compounds 6e and 6g.

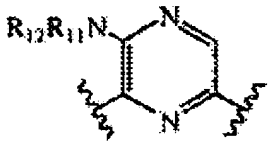
Claims 21-23 and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/87854 (Marchand-Brynaert et al). The Marchand-Brynaert et al reference teaches a family of antioxidant compounds. Pertinent to the chemical entities according to instant claims 21-23 are the compounds of Marchand-Brynaert et al's "formula (I)."

The compound dubbed JFC54, at page 24 is the compound "6g" from the above-cited Cavalier et al reference.

At pages 26-28, several more compounds according to claims 21-23 are disclosed.

Compounds CD29, CD31, CD48, CD51, CD45, CD46, JFC48, JFC58, CD12 CD17, CD22, JFC55, JFC71, JFC72, JFC73 anticipate claims 21-23.

CD29, CD31 (which is the above-cited Cavalier et al's compound 6e), CD51, CD45, CD46 anticipate claims 21-23 where both m=0; Z_1 and Z_2 are both –NH-; R_1 and R_2 are both either substituted phenyl (substituted with one or two hydroxy, or one methoxy); M is



where R_{12} and R_{11} are both hydrogen.

In compounds JFC48, JFC58, CD12, CD17, CD22, JFC55, JFC71, one of the groups corresponding to R_1 or R_2 of instant claims 21-23 is H. These compounds are not excluded by the proviso at the end of the definition of R_1 and R_2. Additionally, compounds JFC55, JFC71, JFC72 and JFC73 have a benzyl substitution at the amino nitrogen on the pyrazine ring in what corresponds to "M" of the instant claims. Benzyl *is* permitted in R_{12} and R_{11}.

A pharmaceutical composition comprising compounds CD46 and CD31 is disclosed at pages 31 and 32 of the reference, in an *in vitro* experiment where the protective effect of those compounds on keratinocytes treated with UVB radiation was

studied. A composition comprising the compound, and a vehicle or carrier is necessarily part of such an experiment. That the composition was biologically compatible indicates that it is "pharmaceutically acceptable" within broadest reasonable interpretation of the term.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/87854 (Marchand-Brynaert et al).

Marchand-Bryanaert et al is applied to claim 15 as set forth above in the rejection of claims 21-23 and 15 under 35 U.S.C. 102(a).

At the time the invention was made, the composition of claim 15 would have been obvious to one of ordinary skill in the art.

In addition to the biological experiment at pages 31 and 32 of the reference, wherein a composition comprising CD46 and CD31 was used, Marchand-Bryanaert et al expressly suggests at pages 12 and 13 that "The present compounds are also useful in human and veterinary medicines for the prevention and the treatment of diseases linked to oxidative damages..."

Given this teaching, one of ordinary skill in the art would find it obvious to make a pharmaceutical composition comprising a compound from Marchand-Bryanaert et al, and a vehicle or excipient.

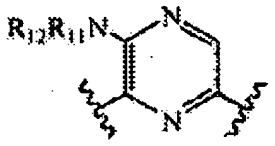
The motivation to make such a composition would have been to enable the treatment of any one of a variety of conditions which are suggested at pages 12 and 13 of the reference, such as ischemia-reperfusion injury, with an antioxidant compound disclosed in Marchand-Bryanaert et al.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The chemical entity of claim 7 is novel and unobvious over the prior art.

A genus of chemical entities based on the elected compound, N3-(2-methoxybenzyl)-5-(4-phenoxyphenyl)-pyrazine-2,3-diamine and a pharmaceutical composition comprising such chemical entities would be allowable.

The examiner suggests the following genus:



, wherein $-(Z_1)_m-R_1$ is the "Z-R" group adjacent to the amino group on the pyrazine ring, and "m" in this group is equal to 1, Z_1 is –NH- and R is benzyl or unsubstituted benzyl, and $-(Z_2)_m-R_2$ is m=0, and R_2 is phenoxyphenyl. R_{11} and R_{12} are as specified in claim 21.

Comments on Information Disclosure Statement

PTO forms 1449 accompanying the IDS filings of 27 January 2005, 8 December 2003 and 11 August 2003 are signed, initialed and enclosed herewith. The examiner would bring to applicants' attention two citations on the PTO 1449 filed 27 January 2005 that appear to have been mistakenly included – DE 197 00 320, which discloses a metal flange, and GB 1,016,202, which discloses swivel nozzles for sheet caliper control of paper.

Applicants should check to see if these were intended to have been cited. The examiner would appreciate it, as IDS filings after notices of allowance, to correct such mistakes, are inconvenient for all parties involved.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 6:00am to 2:30pm, Monday from 6:00am to 1:30pm and Friday from 6:00am to 3:30pm (EST). If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624